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COOPERATIVE AGREEMENT NUMBER DAMD17-94-V-4012

TITLE: PET-FDG Imaging in Metastatic Breast Cancer Treated with High Dose Chemotherapy and Stem Cell Support

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REPORT DATE: August 1998

TYPE OF REPORT: Annual

PREPARED FOR: Commanding General
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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19990928 378

REPORT DOCUMENTATION PAGE

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OMB No. 0704-0188

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1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE August 1998	3. REPORT TYPE AND DATES COVERED Annual (1 Sep 97 - 31 Aug 98)	
4. TITLE AND SUBTITLE PET-FDG Imaging in Metastatic Breast Cancer Treated with High Dose Chemotherapy and Stem Cell Support			5. FUNDING NUMBERS DAMD17-94-V-4012	
6. AUTHOR(S) Doctor Abass Alavi				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Pennsylvania Philadelphia, Pennsylvania 19104-3246			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Commander U.S. Army Medical Research and Materiel Command Fort Detrick, Frederick, Maryland 21702-5012			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200) This study is designed to assess the effectiveness of positron emission tomography (PET) with fluorodeoxyglucose in patients with metastatic breast cancer undergoing high dose chemotherapy with stem cell rescue. It includes patients enrolled on two high dose chemotherapy trials (PBT-1 and UCPP # 3195). So far, 31 patients have been enrolled in the protocol, and the study is proceeding as planned. We have performed a preliminary analysis of the PET studies of 24 patients performed before high dose chemotherapy. In this subgroup of patients, 17 had active disease demonstrated on the PET study, and 7 had no evidence of metabolically active disease. Two subjects had disease involvement demonstrated only on PET imaging and proven at pathology or follow-up. Several repeat studies have been performed and will be analyzed when enough prognostic information becomes available. Patient accrual is ongoing and the study is proceeding as scheduled. PET FDG imaging is a promising tool that can potentially predict early therapeutic failure.				
14. SUBJECT TERMS Breast Cancer			15. NUMBER OF PAGES 24	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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INTRODUCTION

Positron emission tomography (PET) was introduced as a research modality to investigate physiological and biochemical alterations in the brain and heart¹. Many radiopharmaceuticals have been introduced for the study of various organs, but ¹⁸F-fluoro-2-deoxy-2-glucose (FDG) is generally considered the most useful radiopharmaceutical for the diagnosis of various tumors. Breast cancers have enhanced glycolytic activity and have a significant overexpression of glucose transporters². Tumor hypoxia has been shown to increase FDG retention³, and the tracer has been shown to be mainly incorporated in malignant cells⁴.

There are now several reports on studies of patients with breast cancer, suggesting that the PET-FDG technique is effective in diagnosing and following patients with primary and metastatic breast tumors⁵⁻¹⁰. A recent retrospective study on the efficacy of PET in detecting axillary lymph node involvement has suggested potential cost savings by reducing the number of axillary dissections for breast cancer. Almost 74,000 women (75% patients) with primary breast tumors could potentially be spared axillary dissection based on the sensitivity and specificity of PET-FDG imaging to detect lymph node involvement¹¹.

Some groups have reported on the use of PET to evaluate tumor response to therapy. Wahl¹² described the use of PET-FDG for monitoring the treatment response of primary breast cancer. Eleven patients with large primary cancers were studied before chemohormonotherapy and at four times after initiating treatment (at days 8, 21, 42 and 63). The quantitative PET scans showed a rapid decrease in tumor glucose metabolism in all eight patients whose cancers responded clinically, but no change in the 3 non responding patients. Qualitative (visual) analysis gave the

same result. The metabolic change preceded clinical evidence of response (mammographic change), and in some patients the mammogram was difficult to interpret due to dense breast tissue. Thus, the PET-FDG appeared to be an early and accurate predictor of breast cancer response. Huovinen et al¹³, using ¹¹C-Methionine, reported changes in uptake in soft tissue lesions of eight patients treated with chemotherapy, hormone therapy or radiation. The PET responses correlated with clinical responses; uptake increased in those who showed progressive disease, and decreased in patients with stable or improving lesions. Jansson et al¹⁴ studied sixteen patients with locally advanced and metastatic breast cancers receiving chemotherapy. They noted a decrease in uptake (¹¹C-Methionine or FDG) compared to pretreatment scans in eight of twelve responders after the first course of therapy (scans were performed at 6 - 13 days after treatment). Scans done after a third chemotherapy course showed a decrease in all clinical responders. These responses were noted in breast, axillary nodes, pleura and liver.

The purpose of our study was to evaluate the effectiveness of PET-FDG in patients with metastatic breast cancer who are also being treated with high dose chemotherapy and stem cell rescue. The hypotheses of the study were as follow:

- 1) Active tumor sites shown by anatomical imaging methods will be associated with high levels of metabolic activity while inactive sites will be reflected by low levels of FDG uptake.
- 2) Reduction in tumor metabolic activity of tumors will be an early predictor of response to high dose chemotherapy.
- 3) Patients with no abnormal FDG uptake prior to high dose chemotherapy will live longer than patients with tumor that are metabolically active.

The use of PET in this setting is potentially cost-saving considering the high costs of stem cell rescue. Non responders do not need to undergo further chemotherapy with consequent suffering and high costs, when palliation is more appropriate. On the other hand, the ability to predict the response to chemotherapy in responders might enable the physician to modulate the treatment for each patient.

The study included a relatively homogeneous group of patients entered from University of Pennsylvania studies for the treatment of breast cancer with high dose chemotherapy.

BODY

Materials and Methods

Patient Selection:

Patients selected for entry in this study were women accepted from one of several high dose chemotherapy protocols utilizing autologous stem cell support at the University of Pennsylvania. Until January, 1998, the protocols were: UPCC #3195 ("Phase II Pilot Study of High Dose Chemotherapy With Melphalan Followed by Cyclophosphamide, Thiotepa, and Carboplatin with Cyclophosphamide and G-CSF Augmented Peripheral Stem Cell Support For Women With Responding Metastatic Breast Cancer") and Protocol PBT-1 ("Phase III Randomized Comparison of Maintenance Chemotherapy with Cyclophosphamide, Methotrexate and 5-FU vs. High Dose Chemotherapy with Cyclophosphamide, Thiotepa and Carboplatin and autologous bone marrow support for women with metastatic breast cancer who are responding to conventional induction chemotherapy"). These studies were completed and closed. The most recent protocols from which

the patients were recruited were: UPCC #8197 ("Evaluation of Multiple Cycles of High Dose Chemotherapy Supported with Filgrastim and Peripheral Blood Progenitor Cells in Patients with Metastatic Breast Cancer") and UPCC #7197 ("Multi-Institution Study of Docetaxel and Doxorubicin as Induction Therapy Followed by Sequential High Dose Chemotherapy and CD 34+ Selected Stem Cell Support for Women with Metastatic Breast Cancer")

Chemotherapy Studies:

UPCC #3195: This study was a University of Pennsylvania Cancer Center single institutional trial designed for patients with metastatic disease or inflammatory breast cancer. Those patients with no evaluable disease or a documented complete or partial response to standard chemotherapy were treated with high dose sequential chemotherapy and peripheral stem cell rescue. Patients received high dose Cyclophosphamide followed by G-CSF to stimulate stem cell production. This was followed by apheresis to harvest stem cells. When blood count recovery occurred, high dose Melphalan was administered to the patient followed by infusion of one-third of the collected stem cells. Twenty-one days later, the patient was treated with high dose chemotherapy regimen consisting of Cyclophosphamide (1500 mg/m^2), Thiotepa (125 mg/m^2) and Carboplatin (200 mg/m^2), each drug being given daily for four days. This was followed by peripheral stem cell reinfusion.

PBT-1: The purpose of this study was to compare the time to treatment failure, overall survival and toxicity in patients with metastatic breast cancer who were treated with conventional chemotherapy alone or conventional dose chemotherapy followed by high dose chemotherapy and autologous bone marrow rescue. Patients were entered in this trial prior to receiving any chemotherapy for metastatic disease. They then receive Cytosan, Adriamycin and 5-FU. At the

end of 4 - 6 cycles of treatment for metastatic disease, the patients were reevaluated. Those in a partial response or in a complete response were then randomized either to continue the same chemotherapy (or change from Adriamycin to Methotrexate after a total dose of Adriamycin has been given) until relapse or to receive high dose therapy and autologous bone marrow treatment with no further therapy after the transplant. The high dose regimen consisted of 4 days of Cyclophosphamide (1500 mg/m^2), Thiotepa (125 mg/m^2) and Carboplatin (200 mg/m^2). The patients who were considered for bone marrow transplantation were selected for this PET study.

UPCC #8197: This study is a multi-center trial designed to investigate the efficacy of administering a regimen consisting of cyclophosphamide and paclitaxel and Filgrastim to mobilize peripheral blood progenitor cells, followed by two cycles of carboplatin and paclitaxel followed by a cycle of melphalan, each supported with previously mobilized peripheral blood progenitor cells and Filgrastim, in patients with metastatic breast cancer.

UPCC #7197: This is a multi-center study to assess the toxicity and response rates to induction docetaxel and doxorubicin in women with metastatic breast cancer previously untreated with chemotherapy for metastatic disease.

PET Imaging:

The PENN PET 240H camera, manufactured by UGM, was used extensively for FDG and ^{15}O -water brain studies, FDG whole-body cancer studies, and FDG/ ^{13}N -ammonia cardiac studies. This scanner was based on NaI(Tl) position-sensitive detectors, which leads to high spatial resolution, 5.5 mm (FWHM) in the transverse and axial directions, and fine spatial sampling, 2 mm in both the transverse and axial directions¹⁵. The fine axial sampling, in particular, was a

unique advantage of the system, leading to a maximum of 64 slices, which helped us achieve accurate quantification and reduce the partial volume effect in PET¹⁶. To achieve the maximum sensitivity, the scanner operated as a full-time 3D system, without septa.

In August, 1998, we began using a new scanner for FDG-PET imaging. The new C-PET scanner is a whole-body camera, with a transverse field-of-view of 56 cm and axial field-of-view of 25 cm. The intrinsic spatial resolution in the center of the field-of-view is 5 mm, in both the transverse and axial directions. This scanner is unique in its use of six curved NaI(Tl) crystals, arranged with a system diameter of 91 cm, without septa. The use of NaI(Tl) leads to very good energy resolution of 11 % and a relatively low scatter fraction of 25%, as measured with the standard NEMA phantom. The volume sensitivity, with scatter and randoms subtracted, is 400 kcps/uCi/cc, using the same phantom. The maximum true coincidence rate (again, with scatter and randoms subtracted) is 75 kcps, at an activity concentration of 0.3 uCi/cc. Without septa, the data are acquired and reconstructed in 3D. Fourier rebinning is used to sort the 3D data, and an iterative algorithm (OS-EM) is then applied for image reconstruction which requires only 5 seconds per slice on a SUN Ultra Sparc 1 workstation. Corrections for scatter, randoms, and attenuation are applied immediately before image reconstruction. Attenuation correction is performed using a Cs-137 singles source, which rotates in 90 seconds at each bed position. The transmission data is acquired immediately after the emission scan at each bed position, using energy discrimination to separate the transmission events from the emission events. The transmission scan is reconstructed and tissue thresholding is applied before attenuation correction is performed, so as to preserve measured attenuation variations in the lung region and lung/tissue wall. A full body scan (about 100 cm) with attenuation correction can be acquired in under 1 hour

using 8 bed positions, to ensure uniform sensitivity, with 5 minute emission scans and 1.5 minute transmission scans.

With the PENNPET 240H, 114 $\mu\text{Ci/kg}$ FDG was injected intravenously in each patient. Currently, the dose used for the CPET scanner is 68 $\mu\text{Ci/kg}$ FDG. Forty minutes later, the patient is positioned supine in the scanner, feet first, with her arms extended and folded behind the neck and imaging was performed.

We have also implemented an iterative reconstruction algorithm (ordered subsets expectation maximization algorithm) to improve the image quality of whole-body studies and reduce artifacts produced by non uniform distribution of activity, especially in the thorax and the pelvis²⁰. In our analysis of this algorithm, we have clearly shown significant improvements in image quality, with reduction of the noise content of the reconstructed images. Combined with improvements in our techniques of attenuation correction²¹, we are able to achieve optimal quantitative whole-body studies for this protocol. These improvements are applied on all studies acquired for this protocol.

Qualitative interpretation:

The whole-body images were read by two experienced observers with and without attenuation or scatter correction. The readers were blinded to clinical and other radiological information. Regions of the body were considered abnormal according to the following criteria: nodal disease was identified when a clearly defined nodular abnormality could be demonstrated in lymph node groups, exceeding regional average activity; local bone involvement was considered for areas with focally increased tracer uptake higher than maximal marrow activity; diffuse bone marrow

involvement was considered if the tracer retention exceeded that of liver activity; liver and other soft tissue lesions were considered positive if clear nodular areas of increased tracer retention were identified, exceeding regional average activity. Increased areas of tracer retention corresponding to sites of normal physiologic distribution (urinary tract, bowels, muscle groups, heart, thyroid, etc.) were not considered abnormal. The rating scale utilized for recording the abnormalities is indicated in table 1.

Quantification

Quantitative analysis was carried out on attenuation and scatter corrected images by assigning regions of interest (ROI) over the area(s) of abnormal uptake visually determined. One quantitative measure of the uptake of a given isotope in a tumor is the standardized uptake value (SUV)¹⁹ which is defined as:

$$\text{SUV} = (\text{uptake activity/gram of tissue})/(\text{injected activity/gram of patient weight}).$$

In malignant tumors, SUV > 2, sometimes reaching as high as 9-10, whereas in normal tissue SUV \approx 1. Two types of measurements were made with this analysis. One consists of drawing a ROI which will include the entire area of abnormal uptake from which an average SUV for the abnormality is calculated. The other consists of sampling the most active portion of the lesion to determine the maximum activity concentration in the tumor. While the former is used to measure the overall tumor activity, the latter is considered for grading the tumor. We are utilizing these quantitative measurements to monitor disease progression in individual subjects, after high-dose chemotherapy.

Results:

Qualitative interpretation:

Until now, 38 patients have had their initial PET studies before entering their high dose chemotherapy protocol. We have so far analyzed the results of the initial PET examinations in 24 of these patients to assess the prevalence of disease in metastatic breast cancer patients before high dose chemotherapy with stem cell rescue. The results of the PET studies were compared with the results of clinical examination and other radiological data, and are reported in tables 2 - 6.

Seventeen subjects had active disease demonstrated on the PET study (17/24, 81%), and in seven, no evidence of metabolically active disease was noted. In two subjects (8.3%), metastatic disease involvement was shown only on PET imaging (subjects 5, and 20 on table 2). In two subjects (subjects 8 and 24 on tables 2 and 4) with negative PET scans, residual lesions were shown only by bone scanning (8.3%). One of these subjects (subject 8) had a residual rib lesion that had responded well to conventional chemotherapy, and had become sclerotic on x-ray. The overall agreement with the combined restaging procedures was 83% (20/24, 95% confidence interval 68-98%, Kappa statistic 0.60), with FDG-PET demonstrating the presence of unsuspected disease in 2/7 (29%) patients thought to be free of measurable disease at the time of entry in the high dose chemotherapy trial.

Further analysis of the regional sensitivity of FDG-PET imaging indicates that this test is sensitive for detecting lymph node disease in the chest (table 3). In this area, FDG-PET imaging agreed with the conventional assessment in 20/24 subjects (83%, 95% confidence interval 68-94%). FDG-PET demonstrated the presence of hypermetabolic lymph node involvement in the chest in 8/24 patients. Only one of these patients had a positive CT in a corresponding site

(subject 19, table 3), five had negative CT, while one patient had not undergone a restaging chest CT. Six of the eight patients with FDG-PET abnormalities in the mediastinum had evidence of metastatic disease elsewhere.

For the assessment of marrow involvement, FDG-PET was in good agreement with the bone scan results for the overall assessment of the presence of metastases (21/24 subjects, 87.5%, 95% confidence interval 68-97%, Kappa = 0.75). In the evaluation of liver disease, there was moderate overall agreement between PET and CT (17/24, 71%, 95% confidence interval 49-87%, Kappa = 0.26), but with more discrepancies than in other anatomic sites (Table 5).

We have also attempted to assess the accuracy of FDG-PET utilizing short-term outcome (6 months) with clinical and imaging follow-up as a "gold standard". Using these data to calculate the performance of FDG-PET, we obtained a sensitivity of 85% (95% confidence interval 62-97%), a specificity of 100% (40-100%), a positive predictive value of 100% (80 - 100%), and a negative predictive value of 57.1% (18-90%). These results are summarized in table 6.

Conclusion:

Our project ongoing successfully, and patient accrual is proceeding as planned. The initial data analysis confirmed the usefulness of FDG-PET imaging in restaging breast cancer. FDG-PET imaging provides unique independent information about disease activity in patients with breast cancer prior to high dose chemotherapy. The role of FDG PET in establishing prognosis and in assessing the outcome of treatment is being actively studied. Further subject accrual is underway and no difficulties are expected to achieve the goal of 40 subjects before the end of the year. We believe the results of this study will be of considerable importance in the management of patients with breast cancer who are being considered for bone marrow transplantation.

Please see attached abstract for further results.

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TABLE 1: PET qualitative rating scheme

<i>PET Rating scale:</i>	
0:	Normal scan
1:	Probably normal scan
2:	Possibly abnormal scan
3:	Probably abnormal scan
4:	Definitely abnormal scan

Grades 0-1 were considered negative, and 2-4 positive.

TABLE 2: FDG-PET imaging in the assessment of residual disease compared to combined clinical evaluation and conventional imaging procedures

No	PET result	PET Grade	Other Imaging	Global clinical
1	+	4	+	R
2	+	4	+	R
3	-	1	-	ND
4	-	0	-	ND
5	+	4	-	ND
6	+	4	+	R
7	+	4	+	R
8	-	1	+	R
9	+	3	-	ND
10	+	4	+	R
11	+	3	+	R
12	+	4	+	R
13	-	1	-	ND
14	-	1	-	ND
15	+	4	+	R
16	+	4	+	R
17	-	0	-	ND
18	+	3	+	R
19	+	3	+	R
20	+	4	-	ND
21	+	3	+	R
22	+	4	+	R
23	+	4	+	R
24	-	0	+	R

“=”: Equivocal result

“+”: Positive result

“-”: Negative result

“R”: Partial response to previous chemotherapy

“ND”: No demonstrable disease

2x2 Table

FDG-PET	Clinical/Imaging		Total
	+	-	
+	15	2	17
-	2	5	7
Total	17	7	24

TABLE 3 – Assessment of thoracic disease

No	FDG-PET				CT/Chest x-ray			
	Lungs	Grade	Nodes	Grade	Chest CT?	Lungs	Nodes	Extent
1	-	0	+	4	y	-	-	PET>CT
2	-	1	-	0	n	-	-	=
3	-	0	-	0	y	-	-	=
4	-	0	-	0	y	-	-	=
5	-	0	+	4	y	-	-	PET>CT
6	-	0	+	4	y	+	-	PET>CT
7	-	0	+	4	y	-	-	PET>CT
8	-	1	-	0	y	-	-	=
9	-	0	+	3	y	+	-	PET>CT
10	-	0	-	0	y	-	-	=
11	-	0	-	0	y	-	-	=
12	-	0	+	4	y	+	-	PET>CT
13	-	1	-	0	y	-	-	=
14	-	0	-	1	n	-	-	=
15	-	0	-	0	y	-	-	=
16	-	0	-	0	y	-	-	=
17	-	0	-	0	n	-	-	=
18	+	2	+	3	n	-	-	PET>CxR
19	-	0	+	3	y	-	+	=
20	-	0	-	0	n	-	-	=
21	-	0	-	0	y	-	-	=
22	-	0	-	0	y	-	-	=
23	-	0	-	0	y	-	-	=
24	-	0	-	0	n	-	-	=

* residual 3 mm nodule in upper left lung; the patient had a history of pulmonary metastases that had almost completely disappeared after conventional chemotherapy.

** the CT study was obtained 73 days before the PET study, demonstrating axillary lesions which were surgically excised prior to FDG-PET. The PET scan was positive in the supraclavicular area, which was normal on that CT.

2x2 Table (presence of thoracic disease)

FDG-PET	Clinical/Imaging		Total
	+	-	
+	4	4	8
-	0	16	16
Total	4	20	24

TABLE 4 – Assessment of bone or marrow disease

<i>No</i>	<i>PET result</i>	<i>PET Grade</i>	<i>Bone scan</i>	<i>Extent</i>
1	-	0	-	=
2	+	4	+	BS>PET
3	-	0	-	=
4	-	0	-	=
5	-	0	-	=
6	+	4	+	BS>PET
7	-	0	+	BS>PET
8	-	0	+	BS>PET
9	-	0	-	=
10	+	4	+	=
11	+	3	+	=
12	-	0	-	=
13	-	0	=	=
14	-	0	-	=
15	+	4	+	BS>PET
16	+	4	+	PET>BS
17	-	0	-	=
18	+	3	+	BS>PET
19	-	0	-	=
20	-	0	-	=
21	+	3	+	=
22	+	4	+	PET>BS
23	+	4	+	PET>BS
24	-	0	+	BS>PET

2x2 Table

FDG-PET	Clinical/Imaging		Total
	+	-	
+	<i>10</i>	<i>0</i>	10
-	<i>3</i>	<i>11</i>	14
Total	13	11	24

TABLE 5 – Assessment of liver disease

No	PET result	PET Grade	CT/MR result	Extent
1	-	0	+	CT>PET
2	-	0	+	MR>PET
3	-	0	-	=
4	-	0	-	=
5	-	0	-	=
6	-	0	+	CT>PET
7	-	0	-	=
8	-	0	-	=
9	-	0	-	=
10	-	0	-	=
11	+	2	-	PET>CT
12	+	3	-	PET>CT
13	-	0	-	=
14	-	0	-	=
15	-	0	-	=
16	+	3	+	=
17	-	0	-	=
18	-	0	-	=
19	+	2	+	=
20	+	4	-	PET>CT
21	+	2	+	=
22	+	4	-	PET>CT
23	-	0	-	=
24	-	0	-	=

2x2 Table

FDG-PET	Clinical/Imaging		Total
	+	-	
+	3	4	7
-	3	14	17
Total	6	18	24

Table 6 - combined imaging data with short term follow-up

FDG-PET	Clinical/Imaging/Follow-up		Total
	+	-	
+	<i>17</i>	<i>0</i>	17
-	<i>3</i>	<i>4</i>	7
Total	20	4	24

Sensitivity = 85% (62 - 97%)
 Specificity = 100% (40 - 100%)
 Accuracy = 87.5% (68 - 97%)
 Positive Predictive Value = 100% (80 - 100%)
 Negative Predictive Value = 57% (18 - 90%)

The value reported is the percentage followed by the exact 95% confidence interval

Abstract :

CAN A BASELINE FDG-PET STUDY PREDICT OUTCOME AFTER HIGH DOSE CHEMOTHERAPY IN BREAST CANCER PATIENTS? F. Bénard, A. Alavi, J. Alavi, A. Bhatnagar, S. Hirawat, D. Shnier, E.A. Stadtmauer. Hospital of the University of Pennsylvania, Philadelphia, PA.

FDG-PET imaging has been shown to be an accurate diagnostic test to stage metastatic breast cancer. The purpose of this study was to determine if an abnormal FDG-PET study at entry into a high dose chemotherapy protocol could predict outcome after one year.

Methods: Twenty-one breast cancer patients were enrolled in this study. All subjects underwent FDG-PET scanning before high-dose chemotherapy with autologous stem cell support, and had adequate follow-up with regard to their status at one year after treatment. All patients had responded to previous conventional chemotherapy. A whole-body FDG-PET study was performed before the high dose chemotherapy. The results of the FDG-PET scans, clinical evaluation, and other imaging modalities were compared with outcome after a follow-up period of one year. For this purpose, death, or the presence of residual active disease were considered as unfavorable outcome. The absence of demonstrable disease at one year was considered a favorable outcome.

Results: A positive FDG-PET study tended to be associated with a higher incidence of unfavorable outcome at one year (relative risk = 1.47), although using the Fisher's exact test, the relationship between outcome and the FDG-PET results was not statistically significant ($p = 0.35$). Combining the PET results with those of all other imaging modalities identified patients with a higher risk of unfavorable outcome (relative risk = 1.88), but again, this did not reach statistical significance ($p=0.28$). Power calculations demonstrate that a much larger sample of patients will be needed to demonstrate such a relationship.

Conclusion: Although there appears to be a trend between the presence of active disease (by PET and/or other modalities) before high dose chemotherapy, and unfavorable outcome at one year, other additional factors may influence the outcome. A larger sample of patient enrollment is essential to establish the predictive value of FDG-PET imaging in this setting.